

TRIMETHOPRIM-SULFAMETHOXAZOLE RESISTANCE AND FOSFOMYCIN SUSCEPTIBILITY RATES IN UNCOMPLICATED URINARY TRACT INFECTIONS: TIME TO CHANGE THE ANTIMICROBIAL PREFERENCES

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SUMMARY – Urinary tract infections (UTIs) are among the most common bacterial infections in adult population. They are prevalent in all age groups both in women and men. Also, UTIs are the most frequent indication for empirical antibiotic treatment in emergency department. The aim of this study was to determine the antibiotic resistance rates in the treatment of uncomplicated UTIs. Adult patients admitted to emergency department with uncomplicated UTIs were included in this cross-sectional study. Mid-stream urine samples were obtained under sterile conditions and cultured quantitatively. After 24 hours, the samples showing 10⁵ colony forming unit *per* milliliter (CFU/mL) were tested for antibiotic susceptibility. Resistance to fosfomycin-trometamol (FT), amoxicillin-clavulanic acid (AC), ciprofloxacin (CIP), trimethoprim-sulfamethoxazole (TMP-SMX) and cefpodoxime (CEF) was tested by Kirby-Bauer disc diffusion system. *Escherichia (E.) coli* accounted for the vast majority (93.4%) of the organisms isolated in the study. Among the *E. coli* positive patients, resistance to TMP-SMX was the most common antibiotic resistance. The *E. coli* species detected in our study group were least resistant to FT (2.4%). The resistance rates, especially to CEF, AC and CIP, were significantly higher in patients over 50 years of age. In conclusion, in the treatment of uncomplicated UTIs, TMP-SMX should be excluded from empirical treatment, while fosfomycin could be a viable option in all age groups.

Key words: *Urinary tract infections – drug therapy; Drug resistance, microbial; Fosfomycin – therapeutic use; Trimethoprim, sulfamethoxazole drug combination – therapeutic use; Emergencies*

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections in adult population. In the United States, there are nearly 10 million outpatient visits for UTIs annually. Almost one-fifth of these visits are to hospital emergency departments.

UTIs are also the most common primary diagnosis in women presenting to emergency departments¹. Acute cystitis and pyelonephritis are the most frequent indications for empirical antibiotic treatment without urine culture, especially in emergency department². However, the success of infection treatment is directly related to rational prescription of antibiotics. Due to the resistance problem, inappropriate use of antibiotics leads universally to high medical expenses. In 2012, the study by Mollahaliloglu *et al.* demonstrated that the most common diagnosis in prescriptions containing antibiotics was “urinary tract infection”. When calculating the cost of prescriptions, they

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observed that antibiotics accounted for 50.7% of the total cost³.

The responsible bacteria in most UTIs are the *Enterobacteriaceae* species. *Escherichia (E.) coli* is the most frequently isolated bacterium with a prevalence rate of 75%-95%. *Proteus mirabilis*, *Klebsiella pneumoniae* and *Staphylococcus saprophyticus* are other frequently observed species in young and healthy women (5%-15%)^{2,4}. In adult male patients, *E. coli* is also the most frequently observed causative organism. *Proteus*, *Klebsiella*, *Serratia*, *Pseudomonas* and other *Enterococcus* species are also isolated in urine cultures, especially in older male patients⁵.

Urinary tract infections are usually described under the headings of complicated and uncomplicated infections because of the need for different treatment strategies. Uncomplicated UTIs are infections of the urinary system in patients without any neurological, functional or anatomical abnormalities and are usually observed in young healthy and non-pregnant women. The risk factors for complicated UTIs include male sex, advanced age, hospitalization, pregnancy, urinary catheter, residual urine in the bladder, functional or anatomical abnormalities of urinary tract, immunosuppression, diabetes mellitus, symptoms lasting for more than seven days, and inappropriate antibiotic treatment⁶. UTIs are very rarely observed in men aged 15-50. However, if pyelonephritis is diagnosed in this age group, it almost always presents a risk factor. Another important thing is that there is usually recurrence of the infection and undetected resistance to antibiotics in most complicated UTIs^{7,8}. Empirical prescription of inappropriate antibiotics is probably the main reason for the increased rates of antimicrobial resistance.

The Infectious Disease Society of America and the European Society for Microbiology and Infectious Diseases Committee have published the latest recommendations for the treatment of uncomplicated UTIs. It is emphasized in the guideline that the recommendations are limited, and must be updated according to the regional antimicrobial resistance rates and patterns. According to the guideline, the first-line treatment options for uncomplicated UTIs include nitrofurantoin monohydrate, trimethoprim sulfamethoxazole, fosfomycin trometamol, and pivmecillinam. It is advised that fluoroquinolones and β -lactam

agents should be reserved for alternative treatments. In case of uncomplicated pyelonephritis, ciprofloxacin, ceftriaxone or trimethoprim sulfamethoxazole should be the first choice².

The aim of this study was to identify causative pathogens of uncomplicated UTIs in adult patients admitted to our emergency department and to provide an updated information about the antimicrobial resistance profile with the most frequently prescribed empirical antibiotics (fosfomycin-trometamol (FT), amoxicillin-clavulanate (AC), ciprofloxacin (CIP), trimethoprim-sulfamethoxazole (TMP-SMX) and cefpodoxime (CEF)) in the Istanbul region.

Materials and Methods

The study was conducted prospectively in a tertiary inner city hospital over a period from April 15 to September 15, 2012, after approval of the Hospital Ethics and Research Committee. Patients over 16 years of age admitted to emergency department with the diagnosis of uncomplicated UTI were enrolled in the study.

Patients with septic shock, pyelonephritis, anatomical or functional anomaly in the urinary tract, malignancy, and immunosuppression were not included in the study. Histories of UTIs or urinary catheterization in the last one month and antibiotic usage for any reason in the last seven days were the other exclusion criteria.

Midstream clean catch urine samples were cultured within one hour quantitatively in 5% Sheep Blood Agar and Eosin Methylene Blue (EMB) plates (bioMerieux, France) with a standard wire loop. Inoculated agar plates were incubated at 37 °C and read after 24 hours. Presence of at least 10⁵ colony forming units *per* milliliter (CFU/mL) single bacterium colonies were accepted as significant bacteriuria. Identification of the bacteria was performed by standard conventional methods. If needed, they were biochemically tested with API system (bioMerieux, France). API 20E was used for oxidase-negative, gram-negative bacilli and API20NE was used for oxidase-positive, gram-negative bacilli.

Antibiotic susceptibilities were tested with Kirby-Bauer disc diffusion system and the results were interpreted according to the methods described in the

Clinical and Laboratory Standards Institute (CLSI) documents⁹. Mueller Hinton Agar (bioMerieux, France), and discs containing 200 mcg FT, 20/10 AC, 5 mcg CIP, 1.25/23.75 mcg TMX-SMX and 10 mcg CEF (Oxoid, UK) were used for testing antibiotic susceptibility, respectively. For the purpose of quality control, *E. coli* ATCC 25922 was used as the standard strain in all assays. In the study, the susceptibility level of the isolated microorganisms against the tested antibiotics was determined as 'susceptible', 'intermediate' or 'resistant' according to the susceptibility zone diameter⁹.

Statistical analysis

The SPSS 20.0 program was used on data analysis. In descriptive statistics, data on the frequency, rate, mean and standard deviation were used. The distribution of variables was checked by Kolmogorov-Smirnov test. Independent-samples t test was used for quantitative analysis of the data. The χ^2 -test was used in the analysis of qualitative data. Fisher test was used when the χ^2 -test conditions could not be reached.

Results

Urine culture samples of patients admitted to emergency medicine department with the diagnosis of uncomplicated UTI were evaluated. Five hundred urine cultures were analyzed during the study period. Three hundred and fifty-five (71%) samples were obtained from female and the rest (29%) were obtained from male patients. The distribution of patients according to age is shown in Table 1. Most of the patients were aged 21-40 (54.4%) (Table 1).

Table 1. Demographic characteristics

	n	%
Gender		
female	355	71
male	145	29
Age (yrs)		
16-20	43	8.6
21-30	155	31.0
31-40	112	22.4
41-50	63	12.6
51-60	52	10.4
61 <	75	15.0

Table 2. Age and gender distribution of urine cultures

	Urine culture				P
	Negative		Positive		
Gender	n	%	n	%	
Female	251	67.3	73	80.2	0.016
Male	122	32.7	18	19.8	
Age (mean ± SD)	39.9±17.2		39.7±16.2		0.862
Age distribution					0.980
16-20	33	8.8	7	7.7	
21-30	116	31.1	27	29.7	
31-40	84	22.5	24	26.4	
41-50	47	12.6	12	13.2	
51-60	36	9.7	8	8.8	
60<	57	15.3	13	14.3	

* χ^2 distribution/independent samples t-test

The urine culture results were negative in 373 (74.6%) patients. Thirty-six (7.2%) samples were considered contaminated and excluded from the study. Significant growth of 10^5 CFU/mL urine was recorded in 91 (18.2%) samples. Seventy-three isolates, representing 80.2% of the total isolates were recovered from female patients, while 18 (19.8%) were isolated from male patients (Table 2). The most common uropathogen isolated from the cultures in the study group was *E. coli* (93.4%). *Proteus* spp. constituted 4.4% of the pathogens, and the rest of the isolates were *Klebsiella* spp. (2.2%) (Table 3).

Bacterial growth in urine samples from female patients was significantly higher as compared with urine samples of male patients ($p=0.002$). The mean age of the culture negative and culture positive patients was 39.9 ± 17.2 and 39.7 ± 16.2 , respectively. The age distribution according to bacterial growth did not show statistically significant difference ($p>0.05$) (Table 2).

Antibiotic susceptibility studies of the isolated pathogens are shown in Table 4. The highest resistance rate was observed to TMP-SMX (36.3%). The pathogens isolated from the study urine samples were least resistant to FT (2.2%).

Comparison of antibiotic resistance rates between male and female patients revealed resistance to FT, CEF and CIP to be significantly higher in male patients, with the calculated p values of 0.004, 0.016 and

Table 3. Distribution of isolates according to gender and age groups

	Isolated pathogen				
	None	<i>E. coli</i>	<i>Klebsiella</i> spp.	<i>Proteus</i> spp.	
Gender	Female	n 251	68	1	4
	%	77.5	21.0	0.3	1.2
	Male	n 122	17	1	0
	%	87.1	12.1	0.7	0.0
Age (yrs)	16-20	n 33	6	1	0
	%	82.5	15.0	2.5	0.0
	21-30	n 116	25	0	2
	%	81.1	17.5	0.0	1.4
	31-40	n 84	21	1	2
	%	77.8	19.4	0.9	1.9
	41-50	n 47	12	0	0
	%	79.9	20.3	0.0	0.0
	51-60	n 36	8	0	0
	%	81.8	18.2	0.0	0.0
	60<	n 57	13	0	0
	%	81.4	18.6	0.0	0.0

Table 4. Antibiotic resistance and susceptibility rates among female and male patients

		Female		Male		P
		n	%	n	%	
Fosfomycin	Susceptible	73	100	16	88.9	0.0004
	Resistant	0	0	2	11.1	
Cefpodoxime	Susceptible	60	82.2	10	55.6	0.016
	Resistant	13	17.8	8	44.4	
Amoxicillin/ clavulanic acid	Susceptible	63	86.3	13	72.2	0.149
	Resistant	10	13.7	5	27.8	
Trimethoprim/ sulfamethoxazole	Susceptible	49	67.1	9	50.0	0.176
	Resistant	24	32.9	9	50.0	
Ciprofloxacin	Susceptible	58	79.5	10	55.6	0.037
	Resistant	15	20.5	8	44.4	

0.037, respectively. Resistance rates to TMP-SMX and AC did not show any statistically significant gender difference (Table 4).

Resistance rates to CEF, CIP and AC were significantly higher in patients older than 50 as compared with those younger than 50. However, there was no statistically significant age difference in the resistance rates to FT and TMP-SMX (Table 5).

Among the female patient urine samples, 68 *E. coli*, 4 *Proteus* spp. and 1 *Klebsiella* spp. were isolated.

Table 6 shows antibiotic resistance patterns of the uropathogens isolated from the samples of female patients. Of the *E. coli* strains cultured in female patient samples, 32.4% showed resistance to TMP-SMX. The CIP, CEF and AC resistance rates in this group were 20.6%, 17.6% and 13.2%, respectively. *E. coli* strains isolated from the samples of female patients were not resistant to FT (0%).

Among the male patient urine samples, 17 *E. coli* strains and 1 *Klebsiella* spp. were isolated. Table 7 il-

Table 5. Antibiotic susceptibility and resistance rates according to age groups

		<50 years		50 years≤		*p
		n	%	n	%	
Fosfomycin	Susceptible	69	98.6	20	95.2	0.410
	Resistant	1	1.4	1	4.8	
Cefpodoxime	Susceptible	61	87.1	9	42.9	0.0
	Resistant	9	12.9	12	57.1	
Amoxicillin/ clavulanic acid	Susceptible	64	91.4	12	57.1	0.0
	Resistant	6	8.6	9	42.9	
Trimethoprim/ sulfamethoxazole	Susceptible	48	68.6	10	47.6	0.080
	Resistant	22	31.4	11	52.4	
Ciprofloxacin	Susceptible	59	84.3	9	42.9	0.0
	Resistant	11	15.7	12	57.1	

* χ^2 -test/Fisher test

illustrates the antibiotic susceptibility studies of the uropathogens cultured in male patient samples. Resistance rates to TMP-SMX and CIP of *E. coli* strains cultured in male patient samples were the same (47.1%). Resistance rates to AC and FT were 29.4% and 11.8%, respectively.

The antibiotic resistance rates of the isolated pathogens in the culture positive patients are shown in Table 8. Of the *E. coli* strains as the most common uropathogens isolated in the study samples, 35.3% were found to be resistant to TMP-SMX. The resistance rates to CIP, CEF, AC and FT were 25.9%, 25.3%, 16.5% and 2.4%, respectively.

Discussion

Uncomplicated UTIs are generally thought of as UTIs occurring in otherwise healthy, young, female and sexually active but non-pregnant patients without an underlying defect in urinary anatomy or renal function¹⁰. Female gender is described as a primary risk factor for UTIs, while some authors even accepted all male UTIs as complicated^{12,5-7,10,11}. In our study, women also constituted the majority of the study group (71.9%); furthermore, 80.2% of the culture positive urine samples collected for the study were obtained from female patients. According to our re-

Table 6. Antibiotic resistance rates of pathogens isolated from female patient samples

		Pathogen growth					
Female patients		<i>E. coli</i>		<i>Klebsiella</i> spp.		<i>Proteus</i> spp.	
		n	%	n	%	n	%
Fosfomycin	Susceptible	68	100	1	100	4	100
	Resistant	0	0	0	0	0	0
Cefpodoxime	Susceptible	56	82.4	0	0	4	100
	Resistant	12	17.6	1	100	0	0
Amoxicillin/ clavulanic acid	Susceptible	59	86.8	0	0	4	100
	Resistant	9	13.2	1	100	0	0
Trimethoprim/ sulfamethoxazole	Susceptible	46	67.6	0	0	3	75
	Resistant	22	32.4	1	100	1	25
Ciprofloxacin	Susceptible	54	79.4	0	0	4	100
	Resistant	14	20.6	1	100	0	0

Table 7. Antibiotic resistance rates of pathogens isolated from male patient samples

Male patients		Pathogen growth			
		<i>E. coli</i>		<i>Klebsiella</i> spp.	
		n	%	n	%
Fosfomycin	Susceptible	15	88.2	1	100
	Resistant	2	11.8	0	0
Cefpodoxime	Susceptible	9	52.9	1	100
	Resistant	8	47.1	0	0
Amoxicillin/ clavulanic acid	Susceptible	12	70.6	1	100
	Resistant	5	29.4	0	0
Trimethoprim/ sulfamethoxazole	Susceptible	9	52.9	0	0
	Resistant	8	47.1	1	100
Ciprofloxacin	Susceptible	9	52.9	1	100
	Resistant	8	47.1	0	0

sults, the overall antibiotic resistance rates observed in male patients were higher as compared to female patients. According to the recent guidelines for optimal treatment of uncomplicated UTIs, it is reasonable to prescribe empirical antibiotics. It is also emphasized that routine urine culture is not usually necessary for uncomplicated UTIs other than pyelonephritis. However, the most important thing is that local antibiotic resistance pattern should be updated periodically according to the isolated uropathogens.

We found that *E. coli* strains remained the predominant pathogen isolated in urine samples^{5-7,10}.

However, the prevalence rates vary from 75% to 95% worldwide, as well as in the previously conducted studies in Turkey¹²⁻¹⁵. In our study, the prevalence of *E. coli* strains isolated from urine samples of the study group was 93.4%. Although there are reports on the high resistance rates of uropathogens to TMP-SMX, it still takes place as a treatment option for UTIs. In many reports, the resistance rates range between 26% and 63%^{12,16-20}. However, it is advised that if local resistance rates exceed 20%, fluoroquinolones should be used instead of TMP-SMX^{2,5,7}. In our study, the overall resistance to TMP-SMX was 36.3%. There-

Table 8. Antibiotic susceptibility studies of isolated uropathogens

All patients		Pathogen growth					
		<i>E. coli</i>		<i>Klebsiella</i> spp.		<i>Proteus</i> spp.	
		n	%	n	%	n	%
Fosfomycin	Susceptible	83	97.6	2	100	4	100
	Resistant	2	2.4	0	0	0	0
Cefpodoxime	Susceptible	65	76.5	1	50	4	100
	Resistant	20	23.5	1	50	0	0
Amoxicillin/ clavulanic acid	Susceptible	71	83.5	1	50	4	100
	Resistant	14	16.5	1	50	0	0
Trimethoprim/ sulfamethoxazole	Susceptible	55	64.7	0	0	3	75
	Resistant	30	35.3	2	100	1	25
Ciprofloxacin	Susceptible	63	74.1	1	50	4	100
	Resistant	22	25.9	1	50	0	0

fore, it seems that TMP-SMX should not be the drug of choice for empirical UTI treatment in our region.

In recent years, fluoroquinolones have become more popular among physicians for the treatment of UTIs. Mollahaliloglu *et al.* report on the 46.4% rate of fluoroquinolone prescription for the diagnosis of UTIs. In their study, the most frequently prescribed quinolone was levofloxacin (23.2%)³. Guneyssel *et al.* also report that fluoroquinolones were the treatment of choice for UTIs. Ofloxacin was the most frequently used drug in their study¹⁷. Caterino *et al.* report that between 1996 and 2005, TMP-SMX prescription rates decreased gradually while the frequency of prescription of fluoroquinolones increased²¹. The antibiotic susceptibility studies showed progressively increasing resistance rates for quinolones in Turkey. For example, Aydin *et al.*²² found 1.6% resistance rate to CIP in 1996; however, in 1999, Sencan *et al.*²³ and in 2001 Sucu *et al.*²⁴ reported on the resistance rates to CIP of 5% and 18%, respectively. The studies conducted between 2000 and 2005 showed 16.8%–39% CIP resistance of *E. coli* strains isolated in UTIs^{14,25–27}. According to our results, the CIP resistance rate was 25.9% in the study group. Therefore, routine prescription of CIP for uncomplicated UTIs cases appears to be questionable in all age groups.

It seems that advanced age is also an important parameter. We found that resistance rates, especially to CEF, AC and CIP, were significantly higher among patients over 50 years compared to younger patients. The resistance rates of uropathogens to CEF, AC and CIP were 57.1%, 42.9% and 57.1%, respectively. Our results are consistent with literature data^{19,28,29}. In our study, CEF, AC and CIP resistance rates in patients younger than 50 were 12.9%, 8.6% and 15.7%, respectively. FT resistance was very low in both groups. It is reasonable to obtain urine culture routinely from patients over 50 years of age. According to our results, CEF, AC, CIP and FT can be prescribed empirically for patients younger than 50 years.

Because of the advantage of single-dose treatment, FT has recently become increasingly preferred by the physicians. The side effect profile is tolerable and patient compliance is generally better than with other drugs. Antibiotic susceptibility testing reports for FT are also promising worldwide. In the literature, resistance rates vary from 0% to 6.9%^{15,26,27,30–32}. In

our study, FT resistance was 2.2% in the study group and the resistance was higher in male patients (11%). The pathogens cultured in the samples of our female patients were all susceptible to FT. According to our results, FT can be preferred for uncomplicated UTIs in males and females of all age groups.

Regional differences were also remarkable in the reports on antibiotic susceptibility testing from Turkey. Tasbakan *et al.* report on the resistance rates of *E. coli* strains of 39%, 11% and 43% to CIP, AC and TMP-SMX, respectively³³. Ay *et al.* report on the resistance rates of 21%, 40% and 42% to CIP, AC and TMP-SMX, respectively³⁴. In the study by Bingöl *et al.*, *E. coli* strains showed 16.8% resistance to CIP and 35% resistance to TMP-SMX³⁵. Our study was conducted in Istanbul, and 35.3% of the *E. coli* strains, which were the most common uropathogens isolated from the samples, were resistant to TMP-SMX. The resistance rates to CIP, CEF, AC and FT were 25.9%, 25.3%, 16.5% and 2.4%, respectively. Therefore, regional differences should also be taken in consideration when deciding on the choice of empirical antibiotics. Local microbiology laboratories should also report their surveillance data periodically.

Conclusion

Resistance rates, especially to CEF, AC and CIP, were significantly higher in patients older than 50. Therefore, it is reasonable to obtain routine urine culture from this group of patients. In the management of uncomplicated UTIs, TMP-SMX should be excluded from empirical treatment, while fosfomycin could be a viable option in all age groups.

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Sažetak

OTPORNOST NA TRIMETOPRIM-SULFAMETOKSAZOL I STOPE OSJETLJIVOSTI NA FOSFOMICIN KOD NEKOMPLICIRANIH INFEKCIJA MOKRAČNOG SUSTAVA – JE LI VRIJEME ZA PROMJENU PREPORUČENIH ANTIMIKROBNIH LIJEKOVA

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Infekcije mokraćnog sustava (*urinary tract infection*, UTI) spadaju među najčešće bakterijske infekcije u odrasle populaciji, a učestale su u svim dobnim skupinama i u oba spola. Isto tako, UTI su najčešća indikacija za empirijsko liječenje antibiotikima u hitnoj službi. Cilj ovoga istraživanja bio je utvrditi stope otpornosti na antibiotike u liječenju nekomplikirane UTI. U ovo poprečno ispitivanje bili su uključeni odrasli bolesnici primljeni na hitni odjel s nekomplikiranom UTI. Uzorci srednjeg mlaza mokraće uzeti su pod sterilnim uvjetima i kvantitativno kultivirani. Nakon 24 sata uzorci koji su pokazivali 10^5 CFU/mL testirani su na osjetljivost na antibiotike. Otpornost na fosfomicin-trometamol (FT), amoksisicilin-klavulansku kiselinu (AC), ciprofloksacin (CIP), trimetoprim-sulfametoksazol (TMP-SMX) i cefpodoxim (CEF) ispitana je pomoću Kirby-Bauerova sustava disk difuzije. Većinu organizama izoliranih u ovom istraživanju činila je *Escherichia (E.) coli* (93,4%). Među bolesnicima pozitivnim na *E. coli* najčešća je bila otpornost na TMP-SMX. Vrste *E. coli* otkrivene u ovoj skupini bolesnika pokazale su najmanju otpornost na FT (2,4%). Stope antibiotske otpornosti, poglavito na CEF, AC i CIP, bile su značajno više u bolesnika starijih od 50 godina. Zaključuje se kako bi u liječenju nekomplikirane UTI trebalo iz empirijskog liječenja isključiti TMP-SMX, dok bi fosfomicin mogao biti koristan u svim dobnim skupinama.

Ključne riječi: *Urinarne infekcije – farmakoterapija; Lijekovi, rezistencija, bakterijska; Fosfomicin – terapijska primjena; Trimetoprim, sulfametoksazol kombinacija lijeka – terapijska primjena; Hitna stanja*